Draft: September 28, 2007

REMARKS/ARGUMENTS

Claim Amendments

Claims 1-55 have been cancelled and claims 56-65 have been added. Support for the new claims is found in the application as filed, for example as summarized in the table below.

Claim	Support
56	Previous claims 39 and 42
57	Previous claim 40
58	Previous claim 41
59	Previous claim 43
60	Page 18, paragraph [099]
61	Previous claim 44
62	Previous claim 46; pages 10-11, paragraphs [063], [064] and [065]; Figures 23A-23C
63	Previous claim 46
64	Previous claim 55
65	Previous claim 53

The claim amendments have been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants submit that no new matter has been entered by the present amendment and entry of the amendments is respectfully requested. The Applicants reserve the right to file any of the cancelled subject matter in a divisional patent application.

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The Official Action dated June 4, 2007 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's comments and place the present application in condition for allowance. Reconsideration is respectfully requested.

35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 45, 46, 48 and 55 under 35 U.S.C. § 112, first paragraph for failing to meet the written description requirement. The Examiner objects to the term "CYP2A6 inhibitors having a lactone structure with a carbonyl moiety". The Examiner alleges that no other detailed, relevant characteristics are specified which would adequately describe other useful CYP2A6 inhibitors having a lactone structure with a carbonyl moiety.

In the claims submitted herewith, the Applicants have cancelled the subject matter of claims 45 and 48 and have limited the subject matter of previous claim 46 (now found in claim 63) to only specifically named compounds by removing the expressions "and related flavones", "analogs thereof" and "derivatives thereof". The Applicants submit that all of the compounds recited in the present claims are clearly defined by name, and therefore, by structure and the relevant characteristics have thus been specified. The Applicants note that claim 55 is directed to only two specifically named compounds, neither of which comprises a lactone structure with a carbonyl moiety, accordingly they submit that the Examiner's inclusion of this claim in this rejection is in error.

In light of the above, the Applicants request that the Examiner's rejection of claims 45, 46, 48 and 55 under 35 U.S.C. § 112, first paragraph be withdrawn.

35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 44 under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of the limitation "two or more of said substances".

The subject matter of claim 44 is now found in claim 60 which includes the recitation "two or more of said substances which selectively inhibits CYP2A6". Claim 55, upon which claim 60 depends, contains the recitation "at least one substance which selectively inhibits CYP2A6" which provides the antecedent bases for two or more substance in claim 60.

In light of the above, the Applicants request that the Examiner's rejection of claim 44 under 35 U.S.C. § 112, second paragraph be withdrawn.

The Examiner has rejected claim 46 for its dependency on claim 45. The subject matter of claim 45 has been cancelled. The subject matter of claim 46 is now in claim 61 which is dependent on new independent claim 55. The Applicants submit that claim 55 provides proper antecedent basis for the subject matter of claim 61.

The Examiner has also rejected claim 46 for use of the expressions "analogs thereof and derivatives thereof" and "related flavones". These expressions have not been used in the claims submitted herewith.

In light of the above, the Applicants request that the Examiner's rejection of claim 46 under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. § 103 (a)

The Examiner has rejected claims 39-46, 48, 52, 53 and 55 under 35 U.S.C. § 103 (a) as being obvious over Fernandez-Salguero et al. (Am. J. Hum. Genet. 57:651-660, 1995, hereinafter "Fernandez-Salguero"), Gonzalez et al. (PCT Patent Application Publication No. WO 95/34679, hereinafter "Gonzalez") and Draper et al. (Arch. Biochem. Biophys. 341:47-61, 1997, hereinafter "Draper"). The Applicants traverse this rejection for the reasons that follow.

The Examiner alleges that Fernandez-Salguero teaches that CYP2A6 has the highest activity in the conversion of nicotine to cotinine. Further, the Examiner alleges that Fernandez-Salguero teaches that, in human liver microsomes, a correlation was found between coumarin 7-hydroxylation, CYP2A6 protein content and oxidation of nicotine to its iminium ion, the intermediate on route to cotinine.

The Applicants note that Fernandez-Salguero does not provide any specific data in support of the Examiner's allegations. In fact, Fernandez-Salguero reports the effect of variations in the CYP2A6 gene sequence only on coumarin 7-hydroxylation. There is no direct teaching of the effect of genetic variations in the CYP2A6 sequence on the metabolism of nicotine to cotinine, nor that CYP2A6 is involved in the metabolism of nicotine to cotinine.

The suggestion in Fernandez-Salguero that CYP2A6 has one of the highest activities in the conversion of nicotine to cotinine is attributed to McCracken et al. Med. Sci. Res. 20:877-878, 1992 (see page 659, column 1 of Fernandez-Salguero). The suggestion in Fernandez-Salguero that, in human liver microsomes, that a correlation was found between coumarin 7-hydroxylation, CYP2A6 protein content and oxidation of nicotine to its iminium ion, the intermediate on route to cotinine, is attributed to Cashman et al. Chem. Res. Toxicol. 5:639-646, 1992 (see page 659, column 2 of Fernandez-Salguero). Copies of both McCracken and Cashman have been enclosed herewith. The Applicants submit that there is no definitive teaching in either of these references that CYP2A6 is the primary enzyme involved in the metabolism of nicotine to cotinine. In fact, at the time the present application was filed, the Applicants submit that there was no clear and unambiguous teaching that inhibition of CYP2A6 would provide an effective method for enhancing inhibition of nicotine metabolism for the treatment of nicotine-related disorders.

With respect to Cashman, while the teachings in the Abstract indicate that the CYP2A6 had been implicated as the major cyctochrome P-450 isoenzyme responsible

for iminium ion formation in the metabolism of nicotine, the teachings in the body of the paper itself report a different conclusion. This conclusion, based on the results reported therein, is summarized on page 645, top of 2nd column, as follows:

> However, the conclusion that P-450 2A6 is largely responsible for cotinine formation does not preclude the involvement of other P-450s in this key step in human nicotine metabolism. In fact, results of another study [Flammang, A. M., Gelboin, H. V., Aoyama, T., Gonzalez, F. J., and McCoy, G. D. (1992) Nicotine metabolism by cDNA-expressed human cytochrome P-450s. Biochem. Arch. 8, 1-8] suggest that other human liver P-450s (i.e. 2B6, 2C9, 2E1, 2F1, and 4B1) play a prominent role in nicotine $\Delta^{1',5'}$-iminium ion formation. We cannot account for the differences in the substrate specificities of the previous study other than to point out that the human P-450 enzymes used were cDNA-expressed proteins and the present studies employed human liver microsomes.

Still further, on page 645, 2nd column, of Cashman, it is stated that:

> While the human pharmacokinetics of nicotine have been extensively studied, the molecular basis for metabolism of nicotine remains unclear.

Accordingly, the Applicants submit that there is no teaching in Cashman that would lead a person skilled in the art to conclusively believe that CYP2A6 is the key enzyme responsible for the conversion of nicotine to cotinine, nor that administration of an inhibitor of this enzyme would provide an effective treatment for the treatment of nicotine-related disorders.

With respect to McCracken, the Applicants note that, contrary to the Examiner's allegation, this paper does not teach that CYP2A6 has the highest activity in the conversion of nicotine to cotinine. It is clear from the data in Tables 1 and 2 of McCracken, that CYP2B6 was found to have the highest activity in the conversion of nicotine to cotinine, followed by CYP2D6, which had the second highest activity.

McCracken further states on page 877, column 1, that

> [a]lthough it is unclear which human P450 isozymes are responsible for the metabolism of nicotine to cotinine, phenobarbitone pre-treatment is associated with increased nicotine formation [Emphasis added].

Since CYP2B6 is not constitutively expressed in the human liver, McCracken suggests that

> [u]nlike CYP2B6, both CYP2A6 and CYP2D6 are constitutive enzymes of the human liver and as such are more likely to contribute to the C-oxidation of nicotine in humans.

Again, McCracken does not provide any teaching that would lead a person skilled in the art to conclusively believe that CYP2A6 is the key enzyme responsible for the conversion of nicotine to cotinine, nor that administration of an inhibitor of this enzyme would provide an effective treatment for nicotine-related disorders.

Gonzalez, describes mutations in the CYP2A6 and CYP2C9 genes. In the background section, Gonzalez teaches that

> the cytochrome P450 isozyme gene, CYP2A6, encodes a protein that metabolizes nicotine and coumarin...

The remaining portions of Gonzalez describe certain variant alleles of the CYP2A6 and CYP2C9 genes and their use in diagnosis and patient screening. There is no specific teaching in Gonzalez that CYP2A6 is the primary enzyme involved in the metabolism of nicotine nor that inhibition of this enzyme would provide therapeutically relevant effects for nicotine-related disorders.

The Applicants submit that at the time the present application was filed, research on identification of the human CYPs involved in nicotine metabolism to cotinine had suggested several enzymes, including CYP2A6, CYP2B6, CYP2C8, CYP2C9,

CYP2D6, CYP2E1, CYP2F1 and CYP4B1 (Flammang et al., Arch. 8: 1–8, 1992; McCracken et al., Med. Sci. Res. 20:877-878, 1992; Nakajima J. Pharmacol. Exp. Ther. 277: 1010–1015, 1996). In 1996, Nakajima conclude that:

> the enzyme responsible to cotinine formation in humans was in controversy.

Further, the review article written by Seaton et al. (Pharmac. Ther. 60:461-500, 1993, hereinafter "Seaton") highlights the complexity of nicotine metabolism and the inconclusiveness of the results from previous studies:

> [N]icotine metabolism, the study of which is complicated by the existences of multiple metabolic pathways, has been, and continues to be, extensively investigated.[...] Due to large variations caused by several critical host factors, these differences in design render comparison of results exceedingly difficult, of not impossible. (page 462, paragraph 1)

Therefore, although it may have been previously suggested that CYP2A6 was one of the enzymes involved in the metabolism of nicotine, as noted above, there were many other CYP enzymes reported to be involved in this biochemical process. A person skilled in the art would understand that it is necessary to inhibit all relevant enzymes involved in the metabolism of nicotine to obtain any possible therapeutically relevant effect, however, it is clear that, based on the teachings available at the time the present application was filed, this person would not have known, without undue experimentation, which enzyme or enzymes should be inhibited to obtain this effect.

Still further, the Applicants submit that it was believed at the time the present application was filed, that nicotine is a toxic compound. See, for example, Seaton, page 462, paragraph 3:

> The extreme toxicity of nicotine permits administration as a bolus of only a few milligrams of the alkaloid, requiring that each of the many pathways of

> nicotine metabolism be investigated at very low concentrations of each metabolite.

The Applicants submit, therefore, that a person skilled in the art would not have even considered inhibition of the metabolism of nicotine as a viable therapeutic avenue for fear of causing increased levels of this toxic chemical in a patient. Still further, as reported on page 476, paragraph 5, of Seaton, even though ethanol administration had been shown to induce nicotine metabolism

> no effect of ethanol ingestion on the rate of nicotine metabolism was observed in human smokers.

This represents yet another reason why a person skilled in the art, at the time the present application was filed, would not have looked to inhibition of nicotine metabolism as a method to treat nicotine-related disorders.

Therefore the Applicants submit that it is clear that, based on the teachings that were available at the time the present application was filed, a person skilled in the art would not have known that inhibition of the metabolism of nicotine by administration of a selective inhibitor of CYP2A6 would provide therapeutically relevant effects for the treatment of nicotine-related disorders. This fact did not become known until the present inventors taught that by administering a selective inhibitor of CYP2A6 to human subjects, a beneficial therapeutic effect could be realized on their smoking behaviour. In particular, as reported in Example 4 and Figures 25, 26 and 27 of the present application as filed, the Applicants have demonstrated that administration of a potent and selective inhibitor of CYP2A6 to smoking patients resulted in a significant increase in plasma nicotine and a significant decrease in the subject's desire to smoke, urge to smoke and in the expectation that a cigarette would be pleasant (see page 47, paragraph [147] of the application as filed).

The Examiner alleges that Draper teach that clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, miconazole and alpha-naphthoflavone are inhibitors of CYP2A6. The Applicants note that Draper was published in May, 1997 which is after the priority date of the present application. Accordingly, Draper is not citable against the claims of the present application. Even if Draper were citable against this application, the Applicants note that Draper teaches that the above-mentioned compounds inhibit the hydroxylation of the 7 position of coumarin and is silent about the effects of CYP2A6 on the metabolism of nicotine. Accordingly, Draper goes no further to provide teaching that inhibition of CYP2A6 would provide therapeutically relevant effects on the metabolism of nicotine to cotinine.

In light of the above, the Applicants submit that the claims submitted herewith are not obvious over the combined teachings of Fernandez-Salguero, Gonzalez and Draper and respectfully request that the Examiners rejection of claims 39-46, 48, 52, 53 and 55 under 35 U.S.C. § 103 (a) be withdrawn.

The Examiner has rejected claims 39-45, 52, 53 and 55 under 35 U.S.C. § 103 (a) as being obvious over Berkman et al. (Biochem. Pharmacol. 50:565-570, 1995, hereinafter "Berkman"), Seaton et al. (Pharmac. Ther. 60:461-500, 1993, hereinafter "Seaton") and Draper et al. (Arch. Biochem. Biophys. 341:47-61, 1997, hereinafter "Draper"). The Applicants traverse this rejection for the reasons that follow.

The Examiner alleges that Berkman teaches that CYP2A6 is the primary enzyme that transforms nicotine to nicotine $\Delta^{1',5'}$-iminium ion. The Applicants submit that, while Berkman <u>suggests</u> that CYP2A6 is <u>one</u> of the enzymes involved in the metabolism of nicotine to cotinine, Berkman does not teach or suggest that inhibition of this enzyme will result in a therapeutically useful treatment for nicotine-related disorders. In fact, the Applicants submit that the teaching in Berkman would lead a person to believe that inhibition of any enzyme involved in the metabolism of nicotine would <u>not</u> provide a

therapeutically useful method for treating nicotine-related disorders. A person skilled in the art, in reviewing the data provided in Table 1, page 568, of Berkman would see that, of the subjects for which the smoking history[1] was known (i.e. subjects A, B. D, I and F) those with the lowest levels of cotinine formation (i.e. patients A, B and F) were the smokers, whereas the non-smokers (i.e. patients D and I) had the highest levels of cotinine formation. Low levels of cotinine indicate that nicotine is not being metabolized to this species, a situation that would be expected to be analogous to the case where a subject has been administered an inhibitor of the primary enzyme involved in the metabolism of nicotine to cotinine. In the results presented in Berkman, these subjects were smokers, a nicotine-related disorder. Accordingly, a person skilled in the art would not have expected, based on the teachings in Berkman that administration of an inhibitor of the primary enzyme involved in nicotine metabolism to cotinine would provide an effective treatment for nicotine-related disorders.

Contrary to the results presented in Berkman, the present Applicants have surprisingly found that when smoking subjects were administered a selective inhibitor of CYP2A6, plasma nicotine levels were increased, cotinine levels did not change and the subjects felt less need to smoke.

Futher, Berkman also teaches that the calculated metabolic clearance of nicotine via cotinine in the liver is only 23% of the total clearance (page 569, column 2). Berkman goes on to suggest that

> the difference between total metabolic clearance and hepatic clearance for (S)-nicotine biotransformation derives from a (yet to be discovered) metabolite or non-hepatic metabolic pathway of (S)-nicotine (page 569, column 2) [Emphasis added].

[1] Table 1 of Berkman refers to Cashman et al. Chem. Res. Toxicol. 5:639-646, 1992 (copy enclosed) for the smoking histories of the listed subjects.

Accordingly, a person skilled in the art, armed with the teaching in Berkman that CYP2A6 might only be responsible for 23% of the total metabolism of nicotine, would not have been lead by these teachings to the administration of an inhibitor of CYP2A6 for the effective therapeutic treatment of a nicotine-related disorder, and further, in light of the results presented in Table 1 of Berkman (*vide supra*), they would not have even expected that inhibition of the metabolism of nicotine to cotinine, by any route, would be therapeutically useful for the treatment of nicotine-related disorders. Clearly there are errors in the results presented in Berkman.

Seaton is a general review of P450 enzymes and the metabolism of nicotine. Passages from Seaton are quoted above. Its overall message is that inhibition of P450 enzymes, in general, can effect nicotine metabolism however, as described above, Seaton highlights the uncertainty at the time the present application was filed in the results from studies on the metabolism of nicotine and in fact does not mention at all that CYP2A6 is the P450 enzyme responsible for the conversion of nicotine to cotinine. As described above, the teachings in Seaton also suggest that a person skilled in the art would not have even considered inhibition of the metabolism of nicotine as a viable therapeutic avenue for treating nicotine-related disorders. Therefore Seaton does not make up the above-mentioned deficiencies in the teachings of Berkman.

Once again, the Examiner alleges that Draper teach that clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, miconazole and alpha-naphthoflavone are inhibitors of CYP2A6. The Applicants note that Draper was published in May, 1997 which is after the priority date of the present application. Accordingly, Draper is not citable against the claims of the present application. Even if Draper were citable against this application, the Applicants note that Draper teaches that the above-mentioned compounds inhibit the hydroxylation of the 7 position of coumarin and is silent about the effects of CYP2A6 on the metabolism of nicotine. Accordingly, Draper goes no further to provide teaching that inhibition of

CYP2A6 would provide therapeutically relevant effects on the metabolism of nicotine to cotinine.

Accordingly, the Applicants again submit that, based on the teachings of Berkman, Seaton and Draper, a person skilled in the art would not have known that inhibition of the metabolism of nicotine by administration of a selective inhibitor of CYP2A6 would provide therapeutically relevant effects for the treatment of nicotine-related disorders. As noted above, this fact did not become known until the present inventors taught that by administering a selective inhibitor of CYP2A6 to human subjects, a beneficial therapeutic effect could be realized on their smoking behaviour (*vide supra*).

In light of the above, the Applicants submit that the claims submitted herewith are not obvious over the combined teachings of Berkman, Seaton and Draper and respectfully request that the Examiners rejection of claims 39-45, 52, 53 and 55 under 35 U.S.C. § 103 (a) be withdrawn.

The Applicants submit that the information provided herein is fully responsive to the Examiner's requests and invites the Examiner to contact Patricia Folkins at 416-957-1683 if any further information is needed.

Early and favorable action on the merits is awaited.

Respectfully submitted,

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